

(10)



Europäisches Patentamt

European Patent Office

Office européen des brevets

(11) Publication number:

**0 230 742
B1**

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: 26.09.90

(51) Int. Cl.⁵: **C 07 C 211/33, A 61 K 31/135**

(21) Application number: **86309631.9**

(22) Date of filing: **10.12.86**

(54) **N,N-dimethyl-1-1-(4-chlorophenyl)cyclobutyl-3-methylbutylamine hydrochloride monohydrate and pharmaceutical compositions containing it.**

(38) Priority: 17.12.85 GB 8531071

(43) Date of publication of application:
05.08.87 Bulletin 87/32

(45) Publication of the grant of the patent:
26.09.90 Bulletin 90/39

(14) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A-0 087 164
DE-A-3 212 682

The file contains technical information
submitted after the application was filed and
not included in this specification

(73) Proprietor: **THE BOOTS COMPANY PLC**
1 Thane Road West
Nottingham NG2 3AA (GB)

(72) Inventor: **Jeffery, James Edward**
81 Greenland Crescent
Chilwell Nottingham (GB)
Inventor: **Whybrow, Derek**
235 Oxclose Lane
Arnold Nottingham (GB)

(74) Representative: **Thacker, Michael Anthony et al**
THE BOOTS COMPANY PLC Patents Section R4
Pennyfoot Street
Nottingham NG2 3AA (GB)

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European patent convention).

Courier Press, Leamington Spa, England.

EP 0 230 742 B1

Description

The present invention relates to *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride which is useful in the treatment of depression.

British Patent Specification 2098602 describes preparative methods which would be suitable for the preparation of the above compound. The present applicants have found that different samples of *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride prepared by methods described in the above identified patent application have variable amounts of water contained therein and that these samples are hygroscopic. It is undesirable that hygroscopic materials are used in the preparation of medicines because of the difficulties inherent in the handling of hygroscopic materials. In the preparation of medicines it is essential that a consistent weight of active ingredient is included in each dosage form and it is difficult to achieve such consistency with active ingredients which are absorbing water from the environment. It has now been found that if *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride is prepared in the form of a monohydrate a non-hygroscopic product is obtained which is suitable for the preparation of capsules, tablets and other pharmaceutical dosage forms. The present invention therefore comprises *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate in which one molecule of water is present for each molecule of *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride, methods for its preparation, pharmaceutical compositions containing it and the use of those pharmaceutical compositions in the treatment of depression.

N,N-Dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate may be prepared by contacting *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride with a medium consisting of or containing water. In a preferred method *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate is prepared by recrystallising *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride from water or a medium containing water, which may be a mixture of water and a water-immiscible solvent (e.g. toluene, xylene or cyclohexane) or a mixture of water and a water-miscible solvent (e.g. acetone, propan-2-ol, industrial methylated (e.g. acetone, propan-2-ol, industrial methylated spirit, 2-ethoxyethanol, tetrahydrofuran, 1,4-dioxane, methyl acetate or 1,2-dimethoxyethane). Alternative methods to prepare *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate include (a) contacting solid *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride, preferably in finely divided form, with a gaseous medium consisting of or containing water vapour and (b) suspending *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in water or a water-containing medium.

N,N-Dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate may also be prepared by treating *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine with hydrochloric acid or a solvent (e.g. acetone or ethanol) containing hydrochloric acid.

The present invention includes pharmaceutical compositions for use in the treatment of depression containing a therapeutically effective amount of *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate in combination with a pharmaceutically acceptable diluent or carrier. These pharmaceutical compositions may take the form of any of the known pharmaceutical compositions for oral, rectal, parenteral or topical administration. Pharmaceutically acceptable diluents and carriers suitable for use in these compositions are well known in the art of pharmacy. The preferred pharmaceutical compositions are tablets or capsules intended for oral administration. Each tablet or capsule may contain 0.5 to 25 preferably 1 to 12.5 milligrams of *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate.

The pharmaceutical compositions of the present invention may be used in the treatment of depression in humans. In such treatment a total of 0.5 to 150 preferably 1 to 50 milligrams of *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate may be administered daily in one or more doses.

The invention will now be illustrated by the following Examples which describe the preparation of *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate. The present applicants have found that *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride, which was prepared by methods described in British Patent Specification 2098602 and which is used as the starting material for Examples 1 to 11 and 14 to 16, is hygroscopic and may contain variable amounts, but less than one molar equivalent, of water.

The products of the Examples hereinafter were characterised by satisfactory elemental (C, H, N, Cl) analyses and by satisfactory analysis for their water content.

When attempts are made to determine the melting point of *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate using conventional laboratory apparatus, it is believed that the sample dehydrates as the temperature is raised and that the melting point observed is that of the dehydrated material.

EP 0 230 742 B1

Example 1

N,N - Dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride (0.5 g) was dissolved in boiling water (5 ml). The solution was filtered whilst hot and the filtrate cooled. The product crystallised from the cooled filtrate and was collected by filtration and dried in vacuo at ambient temperatures to give *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate (m.p. 193—195.5°C).

Example 2

N,N - Dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride (5 g) was dissolved in a boiling mixture of toluene (126 ml) and water (12.6 ml). The solution was filtered whilst hot and the filtrate cooled. The product crystallised from the cooled filtrate and was collected by filtration and dried in vacuo at ambient temperature to give *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate (m.p. 194—196°C).

Example 3

N,N - Dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride (10 g) was dissolved in a boiling mixture of acetone (110 ml) and water (1.2 ml). The solution was filtered whilst hot and the volume of the filtrate reduced by the removal by distillation of 80 ml of solvent. The product was collected from the cooled concentrate by filtration and dried in vacuo at ambient temperature to give *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate (m.p. 195°C).

Examples 4 to 6

A sample (1 g) of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride which had been dehydrated in vacuo at 70°C for 7 hours was dissolved in a boiling mixture of water (0.5 ml) and an organic solvent (4.5 ml). The solution was allowed to cool to ambient temperature and then stored at 4°C for three hours. A solid was collected by filtration, washed with the organic solvent and dried in vacuo at ambient temperature for 18 hours to give *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate the melting point of which is given below.

Ex.	Solvent	Melting point °C
4	industrial methylated spirit	195—198 (shrinks 160)
5	propan-2-ol	195—198 (shrinks 163)
6	2-ethoxyethanol	194—198 (shrinks 166)

Examples 7 to 11

A sample (1 g) of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride which had been dehydrated in vacuo at 70°C for 7 hours was treated with an organic solvent specified below (x ml) and then water (y ml) was added. The mixture was boiled and the resulting solution allowed to cool to ambient temperature and then stored at 4°C for three hours. In Examples 10 and 11 the solution was stored at ambient temperature for 18 hours and crystallisation initiated by reducing the volume of the solution under a stream of air. A solid was collected by filtration, washed with the organic solvent and dried in vacuo at ambient temperature for 18 hours to give *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate the melting point of which is given below.

Ex.	Solvent	x	y	Melting point °C
7	1,2-dimethoxyethane	10	1	196—198 (shrinks 185)
8	xylene	15	1	196—198 (shrinks 166)
9	cyclohexane	30	2	193—197 (shrinks 160)
10	1,4-dioxan	25	1	196—199 (shrinks 160)
11	methyl acetat	25	2	197—202

Examples 12 and 13

A sample (1 g) of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine was treated with 5M hydrochloric acid (1 ml) and the mixture was dissolved in the minimum quantity of a

EP 0 230 742 B1

boiling organic solvent specified below. The resulting solution was allowed to cool to ambient temperature. A solid was collected by filtration, washed with the organic solvent and dried in vacuo at ambient temperature for 18 hours to give *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate the melting point of which is given below.

5

Ex.	Solvent	Melting point °C
12	acetone	194—197
13	ethanol	196—201

10

Example 14

A sample (5 g) of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride was heated with a mixture of toluene (30 ml) and propan-2-ol (3 ml) to 90°C and allowed to cool to 72°C. Water (0.9 ml) was added and the mixture cooled to 25°C and then placed in an ice-water bath for 30 minutes. A solid was collected by filtration, washed with cold toluene and dried by suction at ambient temperature to give *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate [m.p. 193—195°C (shrinks 150—155°C)].

Example 15

A sample (24.1 g) of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride was dissolved in a boiling mixture of water (72 ml) and tetrahydrofuran (7 ml) and the mixture allowed to cool. A solid was collected by filtration and dried at 40°C to give *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate (m.p. 193—195°C).

25

Example 16

A sample (48.2 g) of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride was suspended and stirred with water (145 ml) for 24 hours at 25°C. The solid was collected by filtration and dried by suction at ambient temperature to give *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate (m.p. 191—195.5°C).

30

The non-hygroscopic nature of products prepared in the Examples hereinbefore is illustrated by the following comparative experiment. A sample of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride was dehydrated in a vacuum oven at 60°C for 16 hours and stored in a desiccator over phosphorus pentoxide. Analysis showed that this material contained no water. When the sample was exposed to the atmosphere for one month analysis showed the water content to be approximately 3% corresponding to about 0.6 molar equivalents of water. However, when a sample of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate was exposed to the atmosphere for five months there was no increase in water content showing that no absorption of water had occurred.

40

Claims for the Contracting States: GB DE FR IT BE NL CH SE LU

1. Solid *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate in which one molecule of water is present for each molecule of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride.

2. Pharmaceutical compositions comprising solid *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate in which one molecule of water is present for each molecule of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride together with a pharmaceutically acceptable diluent or carrier.

3. Solid *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate in which one molecule of water is present for each molecule of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride for use in the treatment of depression in humans.

4. A process for the preparation of solid *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate in which one molecule of water is present for each molecule of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride comprising contacting *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride with a medium consisting of or containing water.

5. A process as claimed in claim 4 which comprises recrystallising *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride from a medium consisting of or containing water.

6. A process as claimed in claim 5 in which the medium containing water is a mixture of water and a solvent selected from toluene, xylene, cyclohexane, acetone, propan-2-ol, industrial methylated spirit, 2-ethoxyethanol, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxan or methyl acetate.

7. A process for the preparation of solid *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate in which one molecule of water is present for each molecule of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride as claimed in claim 4 comprising contacting solid *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride with a gaseous medium consisting of or containing water vapour.

8. A process for the preparation of solid *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate in which one molecule of water is present for each molecule of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride as claimed in claim 4 comprising suspending *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride in water or a water-containing medium.

9. A process for the preparation of solid *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate in which one molecule of water is present for each molecule of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride comprising treating *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine with hydrochloric acid or a solvent containing hydrochloric acid followed by isolation of the solid product.

10. Solid *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate in which one molecule of water is present for each molecule of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride for use in the preparation of a medicament for the treatment of depression.

Claims for the Contracting States: AT GR ES

1. A process for the preparation of solid *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate in which one molecule of water is present for each molecule of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride comprising contacting *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride with a medium consisting of or containing water.

2. A process as claimed in claim 1 which comprises recrystallising *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride from a medium consisting of or containing water.

3. A process as claimed in claim 2 in which the medium containing water is a mixture of water and a water-immiscible solvent.

4. A process as claimed in claim 3 in which the water-immiscible solvent is toluene, xylene or cyclohexane.

5. A process as claimed in claim 2 in which the solvent containing water is a mixture of water and a water-miscible solvent.

6. A process as claimed in claim 5 in which the water-miscible solvent is acetone, propan-2-ol, industrial methylated spirit, 2-ethoxyethanol, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxan or methyl acetate.

7. A process for the preparation of solid *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate in which one molecule of water is present for each molecule of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride as claimed in claim 1 comprising contacting solid *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride with a gaseous medium consisting of or containing water vapour.

8. A process for the preparation of solid *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate in which one molecule of water is present for each molecule of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride as claimed in claim 1 comprising suspending *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride in water or a water-containing medium.

9. A process for the preparation of solid *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride monohydrate in which one molecule of water is present for each molecule of *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine hydrochloride comprising treating *N,N* - dimethyl - 1 - [1 - (4 - chlorophenyl)cyclobutyl] - 3 - methylbutylamine with hydrochloric acid or a solvent containing hydrochloric acid followed by isolation of the solid product.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Festes *N,N* - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid - Monohydrat, in dem in Mol kü l Wasser für jedes Mol kü l *N,N* - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid vorhanden ist.

2. Pharmazeutische Zusammensetzungen, enthaltend *N,N* - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid - Monohydrat, in dem ein Molekül Wasser für jedes Molekül *N,N* - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid vorhanden ist, zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Trägerstoff.

3. Festes N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid - Monohydrat, in dem ein Molekül Wasser für jedes Molekül N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid vorhanden ist, zur Verwendung in der Behandlung der Depression beim Menschen.
- 5 4. Verfahren zur Herstellung von festem N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl)cyclobutyl] - 3 - methylbutylamin - Hydrochlorid - Monohydrat, in dem ein Molekül Wasser für jedes Molekül N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid vorhanden ist, bei dem man N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid mit einem Medium in Kontakt bringt, das aus Wasser besteht oder Wasser enthält.
- 10 5. Verfahren nach Anspruch 4, bei dem man N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl)cyclobutyl] - 3 - methylbutylamin - Hydrochlorid aus einem Medium, das aus Wasser besteht oder Wasser enthält, umkristallisiert.
6. Verfahren nach Anspruch 5, bei dem das Medium, das Wasser enthält, eine Mischung von Wasser und einem Lösungsmittel ist, das aus Toluol, Xylol, Cyclohexan, Aceton, Propan-2-ol, industriellem methylierten Alkohol, 2-Ethoxyethanol, 1,2-Dimethoxyethan, Tetrahydrofuran, 1,4-Dioxan oder Methylacetat ausgewählt wird.
- 15 7. Verfahren zur Herstellung von festem N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid - Monohydrat, in dem ein Molekül Wasser für jedes Molekül N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid vorhanden ist, wie in Anspruch 4 beansprucht, bei dem man festes N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid mit einem gasförmigen Medium, das aus Wasserdampf besteht oder Wasserdampf enthält, in Kontakt bringt.
- 20 8. Verfahren zur Herstellung von festem N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid - Monohydrat, in dem ein Molekül Wasser für jedes Molekül N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid vorhanden ist, wie in Anspruch 4 beansprucht, bei dem man N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid in Wasser oder einem wasserhaltigen Medium suspendiert.
- 25 9. Verfahren zur Herstellung von festem N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid - Monohydrat, in dem ein Molekül Wasser für jedes Molekül N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl)cyclobutyl] - 3 - methylbutylamin - Hydrochlorid vorhanden ist, bei dem man N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin mit Chlorwasserstoffsäure oder einem Lösungsmittel, das Chlorwasserstoffsäure enthält, behandelt und anschließend das feste Produkt isoliert.
- 30 10. Festes N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid - Monohydrat, in dem ein Molekül Wasser für jedes Molekül N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid vorhanden ist, zur Verwendung in der Herstellung eines Medikaments zur Depressionsbehandlung.
- 35

Patentansprüche für die Vertragsstaaten: AT GR ES

- 40 1. Verfahren zur Herstellung von festem N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid - Monohydrat, in dem ein Molekül Wasser für jedes Molekül N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid vorhanden ist, bei dem man N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid mit einem Medium in Kontakt bringt, das aus Wasser besteht oder Wasser enthält.
- 45 2. Verfahren nach Anspruch 1, bei dem man N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid aus einem Medium, das aus Wasser besteht oder Wasser enthält, umkristallisiert.
3. Verfahren nach Anspruch 2, bei dem das Medium, das Wasser enthält, eine Mischung von Wasser und einem nicht mit Wasser mischbaren Lösungsmittel ist.
- 50 4. Verfahren nach Anspruch 3, bei dem das nicht mit Wasser mischbare Lösungsmittel Toluol, Xylol oder Cyclohexan ist.
5. Verfahren nach Anspruch 2, bei dem das Lösungsmittel, das Wasser enthält, eine Mischung von Wasser und einem mit Wasser mischbaren Lösungsmittel ist.
- 55 6. Verfahren nach Anspruch 5, bei dem das mit Wasser mischbare Lösungsmittel Aceton, Propan-2-ol, industrieller methylierter Alkohol, 2-Ethoxyethanol, 1,2-Dimethoxyethan, Tetrahydrofuran, 1,4-Dioxan oder Methylacetat ist.
7. Verfahren zur Herstellung von festem N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid - Monohydrat, in dem ein Molekül Wasser für jedes Molekül N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid vorhanden ist, wie in Anspruch 1 beansprucht, bei dem man festes N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid mit einem gasförmigen Medium, das aus Wasserdampf besteht oder Wasserdampf enthält, in Kontakt bringt.
- 60 8. Verfahren zur Herstellung von festem N,N - Dimethyl - 1 - [1 - (4 - chlorphenyl) - cyclobutyl] - 3 - methylbutylamin - Hydrochlorid - Monohydrat, in dem ein Molekül Wasser für jedes Molekül N,N -
- 65

EP 0 230 742 B1

Diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamin - Hydrochlorid vorhanden ist, wie in Anspruch 1 beansprucht, bei dem man N,N - Diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamin - Hydrochlorid in Wasser oder einem wasserhaltigen Medium suspendiert.

9. Verfahren zur Herstellung von festem N,N - Diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamin - Hydrochlorid - Monohydrat, in dem in Molekül Wasser für jedes Molekül N,N - Diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamin - Hydrochlorid vorhanden ist, bei dem man N,N - Diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamin mit Chlorwasserstoffsäure oder einem Lösungsmittel, das Chlorwasserstoffsäure enthält, behandelt und anschließend das feste Produkt isoliert.

Revendications pour les états Contractants: BE CH DE FR GB IT LI LU NL SE

1. Chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine monohydraté, solide, dans lequel une molécule d'eau est présente pour chaque molécule de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine.

2. Compositions pharmaceutiques, caractérisées en ce qu'elles comprennent du chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine monohydraté, solide, dans lequel une molécule d'eau est présente pour chaque molécule de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine, en même temps qu'un véhicule, excipient ou diluant pharmaceutiquement acceptable.

3. Chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine monohydraté, solide, dans lequel une molécule d'eau est présente pour chaque molécule de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine pour l'utilisation en vue du traitement de la dépression chez les êtres humains.

4. Procédé de préparation de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine monohydraté, solide, dans lequel une molécule d'eau est présente pour chaque molécule de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine, caractérisé en ce que l'on met du chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine en contact avec un milieu constitué d'eau ou contenant de l'eau.

5. Procédé suivant la revendication 4, caractérisé en ce que l'on recristallise le chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine dans un milieu constitué d'eau ou contenant de l'eau.

6. Procédé suivant la revendication 5, caractérisé en ce que le milieu contenant de l'eau est un mélange d'eau et d'un solvant choisi parmi le toluène, le xylène, le cyclohexane, l'acétone, le propane-2-ol, l'alcool dénaturé au méthylène, le 2-éthoxyéthanol, le 1,2-diméthoxyéthane, le tétrahydrofurane, le 1,4-dioxane ou l'acétate de méthyle.

7. Procédé de préparation de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine monohydraté, solide, dans lequel une molécule d'eau est présente pour chaque molécule de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine suivant la revendication 4, caractérisé en ce que l'on met du chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine solide en contact avec un milieu gazeux constitué de vapeur d'eau ou contenant de la vapeur d'eau.

8. Procédé de préparation de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine monohydraté, solide, dans lequel une molécule d'eau est présente pour chaque molécule de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine suivant la revendication 4, caractérisé en ce que l'on met du chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine en suspension dans de l'eau ou un milieu contenant de l'eau.

9. Procédé de préparation de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine monohydraté, solide, dans lequel une molécule d'eau est présente pour chaque molécule de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine suivant la revendication 4, caractérisé en ce que l'on traite de la N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine par de l'acide chlorhydrique ou de l'acide chlorhydrique contenant un solvant, traitement suivi de l'isolement du produit solide.

10. Chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine monohydraté, solide, dans lequel une molécule d'eau est présente pour chaque molécule de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine destiné à l'emploi en vue de la préparation d'un médicament pour le traitement de la dépression.

Revendications pour les états Contractants: AT GR ES

1. Procédé de préparation de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine monohydraté, solide, dans lequel une molécule d'eau est présente pour chaque molécule de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 -

EP 0 230 742 B1

méthylbutylamine, caractérisé en ce que l'on met du chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine en contact avec un milieu constitué d'eau ou contenant de l'eau.

2. Procédé suivant la revendication 1, caractérisé en ce que l'on recristallise le chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine dans un milieu constitué d'eau ou contenant de l'eau.

3. Procédé suivant la revendication 2, caractérisé en ce que le milieu contenant de l'eau est un mélange d'eau et d'un solvant non miscible à l'eau.

4. Procédé suivant la revendication 3, caractérisé en ce que le solvant non miscible à l'eau est le toluène, le xylène ou le cyclohexane.

5. Procédé suivant la revendication 2, caractérisé en ce que le solvant contenant de l'eau est un mélange d'eau et d'un solvant miscible à l'eau.

6. Procédé suivant la revendication 5, caractérisé en ce que le solvant miscible à l'eau est l'acétone, l'propane-2-ol, l'alcool dénaturé au méthylène, le 2-éthoxyéthanol, le 1,2-diméthoxyéthane, le tétrahydrofuran, le 1,4-dioxane ou l'acétate de méthyle.

7. Procédé de préparation de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine monohydraté, solide, dans lequel une molécule d'eau est présente pour chaque molécule de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine suivant la revendication 1, caractérisé en ce que l'on met du chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine solide en contact avec un milieu gazeux constitué de vapeur d'eau ou contenant de la vapeur d'eau.

8. Procédé de préparation de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine monohydraté, solide dans lequel une molécule d'eau est présente pour chaque molécule de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine suivant la revendication 1, caractérisé en ce que l'on met du chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine en suspension dans l'eau ou un milieu contenant de l'eau.

9. Procédé de préparation de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine monohydraté, solide, dans lequel une molécule d'eau est présente pour chaque molécule de chlorhydrate de N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine, caractérisé en ce que l'on traite de la N,N - diméthyl - 1 - [1 - (4 - chlorophényl) - cyclobutyl] - 3 - méthylbutylamine par de l'acide chlorhydrique ou de l'acide chlorhydrique contenant un solvant, traitement suivi de l'isolement du produit solide.